***147450** Links

SUPEROXIDE DISMUTASE 1; SOD1

Alternative titles; symbols

SUPEROXIDE DISMUTASE, CYSTOLIC
SUPEROXIDE DISMUTASE, SOLUBLE
SOD, SOLUBLE
SUPEROXIDE DISMUTASE, COPPER-ZINC
INDOPHENOLOXIDASE A; IPOA

Gene map locus 21q22.1

TEXT

What is now called superoxide dismutase was earlier known as indophenoloxidase. When starch gels were stained by the phenazine-tetrazolium technique in the demonstration of protein, in addition to the appearance of blue bands marking the site of the isozymes under investigation, light or achromatic areas appeared. The bands were the effects of a protein that oxidizes tetrazolium dyes in the presence of phenazine and light. Brewer (1967) observed an electrophoretic variant of this protein, which he called 'Morenci,' in 3 generations of a family with presumed male-to-male transmission. Brewer (1967) demonstrated tetrazolium oxidase in several human tissues and classified it as an indophenol oxidase (IPO-A). The physiologic function of the enzyme was not then known. In the dog there was a genetic polymorphism of red cell tetrazolium oxidase (Baur and Schorr, 1969). In man genetic variation appeared to be rare. Baur (cited by Baur and Schorr, 1969) observed an electrophoretic variant of tetrazolium oxidase in a Caucasian mother and 1 of 2 children. Welch and Mears (1972) found an unusually high frequency of a variant in one of the Orkney Islands. By mouse-man cell hybridization, Tan et al. (1973) demonstrated that indophenoloxidase A is determined by a locus on chromosome 21. IPO-A is a dimer and IPO-B, a tetramer; IPO-B is determined by a locus on chromosome 6 (see 147460).

Beckman (1973) referred to this enzyme as superoxide dismutase (SOD) and reported on the frequency of the 'Morenci' phenotype in a population of northern Sweden. Beckman et al. (1973) found 2 isozymes of superoxide dismutase, A and B, in extracts of human tissues. Isozyme A is a soluble form, whereas B is mitochondrial. Isozyme A is lacking from polymorphonuclear leukocytes, and isozyme B from erythrocytes. The presence of hybrid molecules in heterozygotes indicated that SOD-A is a dimer of 2 identical subunits. The 2 allelic forms of SOD-A were designated SOD-A*1 and SOD-A*2. DeCroo et al. (1988) reported an isoelectric focusing technique to look for SOD-A heterogeneity in erythrocytes.

mitochondrial proteins and lipids.

ALLELIC VARIANTS
(selected examples)

.0001 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, GLY37ARG]

This mutation of the SOD1 gene was identified by Rosen et al. (1993) in a family with amyotrophic lateral sclerosis (ALS; 105400).

In assays by transient expression in primate cells of 6 familial ALS mutant enzymes, Borchelt et al. (1994) found a continuum of enzymatic activity bounded by the enzyme carrying the gly85-to-arg mutation (147450.0006), which was inactive, and mutant enzyme G37R, which retained full specific activity but displayed a 2-fold reduction in polypeptide stability. The G37R mutant displayed similar properties in transformed lymphocytes from an individual heterozygous for the G37R and wildtype SOD1 genes; heterodimeric enzymes composed of mutant and wildtype subunits were detected but there was no measurable diminution in the stability and activity of the wildtype subunits. Thus, for mutants such as G37R, either surprisingly modest losses in activity (involving only the mutant subunit) can yield motor neuron death, or alternatively, mutant SOD1 may acquire properties that injure motor neurons by one or more mechanisms unrelated to the metabolism of oxygen radicals.

.0002 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, LEU38VAL]

This mutation of the SOD1 gene was identified by Rosen et al. (1993) in a family with amyotrophic lateral sclerosis (105400).

.0003 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, GLY41SER]

This mutation of the SOD1 gene was identified by Rosen et al. (1993) in a family with amyotrophic lateral sclerosis (105400).

.0004 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, GLY41ASP]

This mutation of the SOD1 gene was identified by Rosen et al. (1993) in a family with amyotrophic lateral sclerosis (105400).

.0005 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, HIS43ARG]

This mutation of the SOD1 gene was identified by Rosen et al. (1993) in a family with amyotrophic lateral sclerosis (105400).

.0006 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, GLY85ARG]

This mutation of the SOD1 gene was identified by Rosen et al. (1993) in a family with amyotrophic lateral sclerosis (105400).

Previous work had demonstrated that high levels of mutant SOD1 linked to ALS, namely G93A (147450.0008) and G37R (147450.0001), produce disease in transgenic mice through an acquired toxic property. Bruijn et al. (1997) found that even low levels of the gly85-to-arg (G85R) mutation cause

motor neuron disease characterized by extremely rapid clinical progression without changes in SOD1 activity. Initial indicators of disease were astrocytic inclusions that stained intensely with SOD1 antibodies and ubiquitin and SOD1-containing aggregates in motor neurons, features common with some cases of SOD1 mutant-mediated ALS. Astrocytic inclusions escalated markedly as disease progressed, concomitant with a decrease in the glial glutamate transporter (GLT1; 600300). The authors concluded that G85R mediates direct damage to astrocytes, which may promote the nearly synchronous degeneration of motor neurons.

Using the G85R mutation in transgenic mouse experiments, Bruijn et al. (1998) demonstrated that neither elimination nor elevation of wildtype SOD1 had any effect on mutant-mediated disease. The fact that aggregates containing SOD1 were common to disease caused by different mutants implied that coaggregation of an unidentified essential component or aberrant catalysis by misfolded mutants underlies, in part, mutant-mediated toxicity.

.0007 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, GLY93CYS]

This mutation of the SOD1 gene was identified by Rosen et al. (1993) in a family with amyotrophic lateral sclerosis (105400).

.0008 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, GLY93ALA]

This mutation (G93A) was identified by Rosen et al. (1993) in a family with amyotrophic lateral sclerosis (105400).

Yim et al. (1996) cloned the G93A mutant and wildtype cDNA of human SOD1, overexpressed them in Sf9 insect cells, purified the proteins, and studied their enzymic activities catalyzing the dismutation of superoxide anions and the generation of free radicals with H(2)O(2) (peroxide) as substrate. They found that both enzymes contain 1 copper ion per subunit and have identical dismutation activity. However, the free-radical-generating function of the G93A mutant, as measured by the spin trapping method, was enhanced relative to that of the wildtype enzyme, particularly at lower peroxide concentrations. This was due to a small, but reproducible, decrease in the value of K(m) for peroxide for the G93A mutant, while the k(cat) was identical for the 2 enzymes. Thus, the ALS symptoms that had been observed in G93A transgenic mice were not caused by the reduction of SOD1 activity with the mutant enzyme; rather, it was induced by a gain-of-function, an enhancement of the free radical-generating function. This is consistent with the x-ray crystallographic studies showing that the active channel of the G93A mutant is slightly larger than that of the wildtype enzyme; thus, it is more accessible to peroxide. Yim et al. (1996) stated that the gain-of-function may provide, in part, an explanation for the association between ALS and SOD1 mutants. See also Kostic et al. (1997)

.0009 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, GLU100GLY]

This mutation of the SOD1 gene was identified by Rosen et al. (1993) in a family with amyotrophic lateral sclerosis (105400). Winterbourn et al. (1995) demonstrated decreased thermal stability of red cell superoxide dismutase carrying the glu100-to-gly mutation for a family with amyotrophic lateral sclerosis. Extracts containing the mutant had an average 68% of normal SOD activity. On heating at 65 degrees centigrade, these extracts lost activity at twice the rate of extracts containing only normal enzyme.

.0010 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, LEU106VAL]

This mutation of the SOD1 gene was identified by Rosen et al. (1993) in a family with amyotrophic lateral sclerosis (105400). Kawamata et al. (1994) identified this mutation in a Japanese family.

.0011 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, ILE113THR]

This mutation of the SOD1 gene was identified by Rosen et al. (1993) in a family with amyotrophic lateral sclerosis (105400). The ile113-to-thr (I113T) substitution (an ATT to ACT basepair change) was found in 3 patients among 56 cases of ALS drawn from a population-based study in Scotland (Jones et al., 1993); all 3 were apparently the result of a new mutation, i.e., they represented sporadic ALS. Jones et al. (1993) suggested that sporadic cases of ALS may be due to de novo mutations or mutations of reduced penetrance.

Jones et al. (1995) found the I113T mutation in 3 sporadic ALS cases and 3 unrelated familial cases of ALS in Scotland. Because of early death of parents of probands, together with illegitimacy in families, some of the apparently sporadic cases may, in fact, have been familial. The average age of onset of patients with the I113T mutation was cited as 61.2 years, with mean survival of 1.6 years.

Hayward et al. (1996) reported 6 additional cases in Scotland with the I113T mutation and the same genetic background (haplotype) despite no evidence of relatedness. Brock (1998) reported that he and his coworkers had found another 3 cases in the north of England with the I113T mutation and the identical genetic background, one that is rare in the general population. In a disorder such as ALS in which environmental factors may interact with the genotype, or indeed other genes interact with the SOD1 gene, the finding is expected.

Kikugawa et al. (1997) performed mutational analyses of the SOD1 gene of 23 patients (3 familial and 20 sporadic) with ALS from the Kii Peninsula of Japan and its vicinity, where a relatively high incidence of familial occurrence of ALS had been observed. In 2 of the 23 patients, they identified heterozygosity for the I113T mutation in exon 4. The I113T mutation had been identified in some familial as well as sporadic cases of ALS as a mutation with low penetrance. The mutation had been reported to be associated with the formation of neurofibrillary tangles and such was a characteristic feature of ALS in the Kii Peninsula.

.0012 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, ALA4VAL]

Deng et al. (1993) found that the ala4-to-val mutation in exon 1 of the SOD1 gene is the most frequent basis for familial amyotrophic lateral sclerosis (105400). This mutation was found in 8 unrelated families. Rosen et al. (1994) confirmed that the ala4-to-val mutation is the most commonly detected of all SOD1 mutations in familial ALS and that it is among the most clinically severe. In comparison with other ALS families, the exon 1 mutation is associated with reduced survival time after onset: 1.2 years, as compared to 2.5 years for all other familial ALS patients.

.0013 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, HIS46ARG]

In 2 Japanese families with unusually slow progression of ALS (105400), Aoki et al. (1993) found an A-to-G transition in exon 2 of the SOD1 gene that resulted in substitution of arginine for histidine-46. His46 is conserved in 15 species ranging from yeast to humans. The mutation was not found in 27 Japanese sporadic ALS patients or in 57 unrelated normal control subjects. Aoki et al. (1993) pointed out that previously identified mutations do not affect conserved amino acids forming the active site, but do reduce SOD1 activity to levels less than half that in normal control subjects. Since Cu/Zn SOD acts

in vivo as a homodimer, the level of enzyme activity less than 50% in heterozygotes probably represents a dominant-negative effect through influence on dimer formation. On the other hand, the level of activity associated with the his46-to-arg mutation was reduced by only about 20%. Aoki et al. (1993) suggested that the his46-to-arg mutation influences only the active site and does not interfere with dimer formation. In the 2 Japanese families with the his46-to-arg mutation, symptoms did not appear in the arms until more than 5 years after onset, and bulbar signs did not appear for more than 8 years after initial symptoms in the legs. The mean survival after onset was 17.3 years in the Japanese cases as compared with 1.5 years and 2.4 years in Caucasian families and 2.5 years in other Japanese families. Aoki et al. (1994) presented in greater detail the data reported by Aoki et al. (1993).

Liu et al. (2000) determined that SOD1 carrying the his46-to-arg mutation binds neither Cu(2+) nor Co (2+) at the native copper-binding site, but forms a new copper-binding site at its surface, near the site of dimer formation.

.0014 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, ALA4THR]

Kawamata et al. (1994) made reference to a Japanese family with ALS (105400) associated with a GCC-to-ACC transition in codon 4 of the SOD1 gene resulting in substitution of threonine for alanine. Nakano et al. (1994) reported this family in full. See 147450.0012 for the ala4-to-val mutation involving the same codon.

.0015 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL, AUTOSOMAL RECESSIVE [SOD1, ASP90ALA]

Prior to the report by Andersen et al. (1995), 20 or more SOD1 mutations in heterozygous state (dominantly inherited) had been reported as the cause of familial amyotrophic lateral sclerosis (ALS; 105400) and patients showed decreased enzymic activity. Andersen et al. (1995) found homozygosity for an exon 4 mutation of SOD1, asp90 to ala (D90A) , in 14 patients among 4 unrelated ALS families and 4 apparently sporadic ALS patients from Sweden and Finland. The erythrocyte SOD1 activity was essentially normal. The findings suggested that this mutation caused ALS by a gain of function rather than by loss, and that the asp90-to-ala mutation was less detrimental than previously reported mutations. Consanguinity was present in several of the families. The age of onset of symptoms ranged from 37 to 94 years in 1 family in which all patients showed very similar disease phenotypes; symptoms began with cramps in the legs, which progressed to muscular atrophy and weakness. Upper motor neuron signs appeared after 1-4 years disease duration in all patients and none of the patients showed signs of intellectual impairment. In a second family, onset in 2 sibs was at the age of 40, with a phenotype like that in the first family. In a third family, 3 sibs had onset at ages 20, 36, and 22 years, respectively. Thus, familial ALS due to mutation in the SOD1 gene exists in both autosomal dominant and autosomal recessive forms. Al-Chalabi et al. (1998) concluded that a 'tightly linked protective factor' in some families modifies the toxic effect of the mutant SOD1, resulting in recessive inheritance.

Aguirre et al. (1999) found the D90A mutation in heterozygous state in affected members of 2 families and in 1 apparently sporadic case of ALS. Direct sequencing of exons 1, 2, 3, 4, and 5 showed no additional mutations in the SOD1 gene in these patients and the D90A mutation was not found on 150 normal chromosomes. Robberecht et al. (1996) found the D90A mutation in a patient with nonclassic features of ALS.

In 2 sibs with ALS from a family described by Khoris et al. (2000), Hand et al. (2001) identified compound heterozygosity in the SOD1 gene: D90A and a G-A shift resulting in an asp96-to-asn

substitution (D96N; 147450.0032). A third sib with the disease died before testing. Further examination of the family identified the D90A mutation alone in 2 unaffected members and the D96N mutation alone in 4 unaffected members. There were no individuals homozygous for either mutation, and no unaffected individual with both mutations was identified. Hand et al. (2001) concluded that both mutations, which occur in the same region of the protein, are required for disease. The authors emphasized that this is the first report of compound heterozygosity for the SOD1 gene in an ALS patient and suggested that the findings may have implications for the interpretation of inheritance patterns in ALS families.

.0016 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL, AUTOSOMAL RECESSIVE [SOD1, ILE104THE]

In a Japanese family transmitting amyotrophic lateral sclerosis (105400) with marked phenotypic variability, Ikeda et al. (1995) identified a novel A-to-T missense mutation in exon 4 of the SOD1 gene that predicts replacement of isoleucine at codon 104 by phenylalanine. The enzymatic activity of copper/zinc SOD in erythrocyte lysates was decreased by 43%. Both upper and lower motor neuron signs were present in affected members. Age of onset varied from 6 to 55 years. Initial symptoms occurred either in the lower or the upper extremities. The duration of the disease varied from 3 to 38 years. Two individuals with this mutation were asymptomatic at age 59 and 34 at the death from other causes though each had affected offspring. The predicted amino acid substitution occurred within a highly conserved loop VI Greek key domain which has also been affected by several other mutations that associated with familial amyotrophic lateral sclerosis, including leu106-to-val (147450.0010) and ile113-to-thr (147450.0011).

.0017 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, LEU144SER]

Sapp et al. (1995) reported a leu144-to-ser mutation in a family with apparently slow progression of amyotrophic lateral sclerosis (105400). This mutation is in close proximity to the active center of the SOD1 enzyme at arginine 143.

.0018 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, ALA145THR]

Sapp et al. (1995) reported an ala145-to-thr mutation of the SOD1 gene in a family with amyotrophic lateral sclerosis (105400).

.0019 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, IVS4AS, T-G, -10, 9-BP INS]

Sapp et al. (1995) discovered a single basepair change in intron 4 immediately upstream of exon 5 of the SOD1 gene in a family with amyotrophic lateral sclerosis (105400). The alternatively spliced mRNA conserves the open reading frame of exon 5, producing a SOD1 protein with 3 amino acids (phe-leu-gln) inserted between exons 4 and 5 following residue 118.

.0020 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, CYS6PHE]

Morita et al. (1996) identified a novel 2-bp mutation in exon 1 of copper zinc superoxide dismutase in a 59-year-old woman who developed rapidly progressive ALS (105400) beginning at age 59. The mutation predicts substitution of a highly conserved cystine residue with phenylalanine. SOD1 activity in erythrocytes was 25.3% of that in controls. Since the only other affected family member was the deceased father, segregation of the mutation with the disorder was not confirmed.

.0021 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, THR151ILE]

Kostrzewa et al. (1996) identified a T-to-C transition at codon 151 of exon 5 of the SOD1 gene, resulting in substitution of an isoleucine for a threonine. The SOD1 mutation was found in a woman with ALS (105400) that had its onset at 48 years of age with progressive dysarthria and dysphagia followed 9 months later by distal weakness of the legs, and then weakness of her left hand. The mutation appeared to affect formation of dimers of the protein and was the most C-terminal amino acid change in SOD1 described to that time.

.0022 AMYOTROPHIC LATERAL SCLEROSIS, SPORADIC [SOD1, GLU21LYS]

Since familial and sporadic ALS (105400) are clinically indistinguishable, Jones et al. (1994) screened for mutations in the SOD1 gene of 56 unrelated, apparently sporadic ALS patients who were identified in a population-based study in Scotland. Direct PCR analysis revealed a novel mutation, a G-to-A transition resulting in a substitution of lysine for glutamic acid at position 21. Glu21 is highly conserved in many organisms. This nucleotide change destroys a TaqI restriction site. The G-to-A transition occurs at a CpG dinucleotide and may have arisen via deamination of methylcytosine, a fairly common type of mutation in human DNA. The discovery of mutations in a gene responsible for removing superoxide free radicals suggests that sporadic ALS, like familial ALS, has a genetic basis and implicates free radical damage as a central event in the pathogenesis of the disease.

.0023 MOTOR NEURON DISEASE, FAMILIAL [SOD1, SER134ASN]

In a 65-year-old Japanese man, who had first noted muscle weakness right lower limb at age 63, Watanabe et al. (1997) found an S134N mutation in the SOD1 gene. The proband's younger brother was also affected with onset of muscle weakness at age 52 with rapid progression of symptoms thereafter and died of respiratory disease 9 months after onset. Both patients showed no upper motor neuron signs throughout the course of the disease and were therefore thought to have adult spinal muscular atrophy. Both parents died of disorders other than neurologic diseases at ages 84 and 49, respectively. Other relatives of the patient had no similar neurologic disease. Because there were no affected females in this family, the diagnosis of X-linked spinal and bulbar muscular atrophy could not be excluded on clinical grounds but was excluded by DNA analysis.

.0024 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, LEU84VAL]

In a Japanese family with 4 members affected by ALS (105400) in 3 generations, Aoki et al. (1995) observed an L84V mutation in the SOD1 gene. The enzymatic activity of Cu/Zn SOD of skin fibroblasts was reduced to 75% of the control level in the affected proband. The progression of the disease was very rapid, but the age of onset varied with sex and with generation within the family. The proband first noted weakness and atrophy in the left hand at age 38 years. Within 3 months, weakness developed in all 4 extremities and he died of pneumonia 1.5 years after the onset of the disease.

.0025 AMYOTROPHIC LATERAL SCLEROSIS, SPORADIC [SOD1, GLY16SER]

In a patient with onset of symptoms at the age of 18 and rapid progression of amyotrophic lateral sclerosis (105400), Kawamata et al. (1997) demonstrated a nucleotide transition converting codon 16 of the SOD1 gene from GGC (gly) to AGC (ser). By 18 years of age, after noting difficulty in writing, muscular weakness progressed rapidly and the patient could not walk unassisted. At the age of 19, he complained of dyspnea and needed mechanical ventilation.

.0026 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, LEU126TER]

In a 58-year-old male with a family history of ALS (105400) and with a personal history of progressive muscle weakness and atrophy for 4 years, Zu et al. (1997) found a T-to-A transition that converted codon 126 of SOD1 from leucine to stop. The mutation resulted in the truncation of most of the polypeptide segment encoded by exon 5 and resulted in a FALS phenotype similar to that observed in patients with missense mutations in the SOD1 gene, establishing that exon 5 is not required for the novel toxic functions of mutant SOD1 associated with ALS. The mutant enzyme was present at very low levels in the patient, suggesting elevated toxicity compared to mutant enzymes with single site substitutions. This increased toxicity probably arose from the extreme structural and functional changes in the active site channel, beta-barrel fold, and dimer interface observed in the mutant enzyme, including the loss of native dismutase activity. In particular, the truncation of the polypeptide chain dramatically opens the active site channel, resulting in a marked increase in the accessibility and flexibility of the metal ions and side chain ligands of the enzyme active site. Zu et al. (1997) proposed that these structural changes cause a decrease in substrate specificity and an increase in the catalysis of harmful chemical reactions such as peroxidation.

.0027 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, IVS4AS, A-G, -11]

In a 72-year-old male with a family history of ALS (105400) and slowly progressive symptoms of muscle weakness and atrophy, Zu et al. (1997) found an intronic mutation (A-to-G) in SOD1 at the nucleotide 11 bases upstream from the intron-junction of exon 5. This splicing junction mutation resulted in alternative splicing in the mRNA with truncation of most of the polypeptide segment encoded by exon 5. The consequences were thought to be similar to those of the leu126-to-ter mutation (147450.0026).

.0028 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL [SOD1, GLY72SER]

Orrel et al. (1997) found a heterozygous gly72-to-ser mutation in exon 3 of the SOD1 gene in a brother and sister with ALS (105400). The brother had onset at age 47 with weakness of the right foot; the sister had died with a diagnosis of ALS at the age of 49 years. This was the first exon 3 mutation to be described; over 50 different mutations involving exons 1, 2, 4, and 5 had previously been described.

.0029 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL, SLOWLY PROGRESSING [SOD1, GLY12ARG]

Penco et al. (1999) found a missense mutation, gly12 to arg (G12R), in exon 1 of the SOD1 gene in a 67-year-old patient with familial ALS (105400). The mutation occurs in the region outside the active site of the enzyme and may lead to local distortion strain in the protein structure. The enzymatic activity of the mutated SOD1 was 80% of normal. The clinical course was unusually slowly progressive. Onset of the disorder occurred at the age of 63. The patient's father had died at age 59 with a diagnosis of ALS recognized during the last year of his life. His clinical features were very similar to those observed in the proband. His first symptoms were walking difficulties associated with weak leg muscles. Tendon reflexes were markedly hyperactive, but Achilles reflexes were absent. Hand and bulbar involvement started late in the course of the illness.

Penco et al. (1999) had originally identified this mutation as GLY12ALA. Gellera et al. (2001) pointed out that the mutation was in fact a change from GGC (gly) to CGC (arg). They likewise described a patient with slowly progressive ALS due to a G12R substitution in exon 1 of the SOD1 gene.

.0030 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL, SLOWLY PROGRESSING [SOD1, PHE45CYS]

In a familial case of slowly progressing ALS (105400), Gellera et al. (2001) found a de novo T-to-G transversion (TTC-TGC) in exon 2 of the SOD1 gene, resulting in a phe45-to-cys substitution (F45C). Onset occurred at 59 years of age, in the distal muscles of the upper limbs.

.0031 AMYOTROPHIC LATERAL SCLEROSIS, SPORADIC [SOD1, HIS80ALA]

Alexander et al. (2002) reported a sporadic case of ALS (105400) in which the evidence for a novel mutation was compelling. A previously healthy 24-year-old man presented with a 4-month history of left leg weakness. Over the subsequent 8 months, his weakness rapidly progressed to involve all 4 limbs and bulbar musculature, manifesting as quadriplegia, dysarthria, and dysphagia. There was no family history of any form of neuromuscular disorder. He died from pneumonia 18 months after the onset of symptoms. Neuropathologic examination showed anterior horn cell degeneration, prominent gliosis, and Bunina bodies in both the spinal cord and brain stem. There was no involvement of the corticospinal tract. Ubiquinated inclusions were demonstrated within anterior horn cells, and SOD1-immunoreactive inclusions were identified. Heterozygosity for an A-to-G transition at nucleotide 112 of exon 4 was discovered. This transition was predicted to result in a his80-to-ala (H80A) amino acid substitution in the SOD1 protein. The unusually young age of the patient permitted the study of DNA from both parents, the maternal grandfather, and his 2 sibs. None of these individuals carried the mutated gene. Paternity and maternity were confirmed by a combination of 10 highly polymorphic short tandem repeats (STRs). The H80A mutation was not identified in DNA from 150 unaffected Irish controls.

.0032 AMYOTROPHIC LATERAL SCLEROSIS, FAMILIAL, AUTOSOMAL RECESSIVE [SOD1, ASP96ASN]

In 2 sibs with ALS (105400) from a family described by Khoris et al. (2000), Hand et al. (2001) identified compound heterozygosity in the SOD1 gene: D90A (147450.0015) and a G-A shift resulting in an asp96-to-asn substitution (D96N). A third sib with the disease died before testing. Further examination of the family identified the D90A mutation alone in 2 unaffected members and the D96N mutation alone in 4 unaffected members. There were no individuals homozygous for either mutation, and no unaffected individual with both mutations was identified. Hand et al. (2001) concluded that both mutations, which occur in the same region of the protein, are required for disease. The authors emphasized that this is the first report of compound heterozygosity for the SOD1 gene in an ALS patient and suggested that the findings may have implications for the interpretation of inheritance patterns in ALS families.

SEE ALSO

Beckman and Holm (1975); Carter et al. (1976); Cox et al. (1980); Crosti et al. (1981); Francke and Taggart (1979); Frants et al. (1975); Hallewell et al. (1985); Lee et al. (1985); Leschot et al. (1981); Philip et al. (1978); Ritter and Wendt (1971); Sherman et al. (1983); Sinet et al. (1976); Tainer et al. (1983); Yoshimitsu et al. (1983)

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***191160** Links

TUMOR NECROSIS FACTOR; TNF

Alternative titles; symbols

TUMOR NECROSIS FACTOR, ALPHA; TNFA
CACHECTIN
TNF, MONOCYTE-DERIVED
TNF, MACROPHAGE-DERIVED

Gene map locus 6p21.3

TEXT

DESCRIPTION

Tumor necrosis factor is a multifunctional proinflammatory cytokine, with effects on lipid metabolism, coagulation, insulin resistance, and endothelial function.

CLONING

Activated macrophages constitute the major cellular origin of TNF, whereas the partially homologous lymphokine lymphotoxin (TNFB; 153440) is derived from lymphoid cells. TNF is associated with in vivo and in vitro killing of tumor cells. It was originally discovered in the sera of mice and rabbits injected first with Mycobacterium bovis strain bacillus Calmette-Guerin (BCG) and then with endotoxin. Serum from such animals produced hemorrhagic necrosis and in some instances complete regression of certain transplanted tumors in mice. Pennica et al. (1984) identified a monocyte-like human cell line that provided a source of TNF and its messenger RNA. cDNA clones were isolated, sequenced, and translated in E. coli. See Wang et al. (1985).

Old (1985) recounted the series of observations, experiments and discoveries that led up to definition of human TNF and cloning of the gene. He referred to cloning as 'an important rite of passage for biological factors such as TNF, and there is a growing sense that a factor has to be cloned before it is taken very seriously.' He paraphrased Descartes: 'It's been cloned, therefore it exists.' Four exons code for a precursor product of 230 amino acids and a mature product of 157 amino acids after an unusually long leader sequence has been removed.

TNFA and TNFB have similar biologic activities and share 30% amino acid homology.

GENE FUNCTION

showed that both TNFA and TNFB map to the 6p23-q12 segment. Nedwin et al. (1985) speculated that close situation of these 2 loci to HLA 'may be useful for a coordinate regulation of immune system gene products.' By Southern blot analysis of a panel of major histocompatibility complex deletion mutants, Spies et al. (1986) established that TNFA and TNFB are closely linked and situated in the MHC either between HLA-DR (see 142860) and HLA-A (142800) or centromeric of HLA-DP (see 142858). By in situ hybridization, they assigned TNFA and TNFB to 6p21.3-p21.1. By pulsed field gel electrophoresis, Carroll et al. (1987) showed that the TNF genes are located 200 kb centromeric of HLA-B (142830) and about 350 kb telomeric of the class I cluster. The TNFA and TNFB genes are separated by 1 to 2 kb of DNA. By hybridization to fragments of NruI-digested DNA, Ragoussis et al. (1988) demonstrated that the TNFA/TNFB genes lie between C2 of class III and HLA-B of class I.

Nedospasov et al. (1986) showed that, in the mouse, TNFA and TNFB are likewise tandemly arranged and situated on chromosome 17, which bears much homology of synteny with chromosome 6 of man. Muller et al. (1987) mapped both tumor necrosis factor and lymphotoxin close to H-2D in the mouse major histocompatibility complex on chromosome 14. By pulsed field gel electrophoresis, Inoko and Trowsdale (1987) showed that the human TNFA and TNFB genes are linked to the HLA-B locus, analogous to their position in the mouse, where they are located between the class III region and H-2D. However, the distance between the TNF genes and the class I region was much greater in man, namely, about 260 kb, compared to 70 kb in the mouse.

ANIMAL MODEL

Bruce et al. (1996) used targeted gene disruption to generate mice lacking either the p55 or the p75 TNF receptors; mice lacking both p55 and p75 were generated from crosses of the singly deficient mice. The TNFR-deficient (TNFR-KO) mice exhibited no overt phenotype under unchallenged conditions. Bruce et al. (1996) reported that damage to neurons caused by focal cerebral ischemia and epileptic seizures was exacerbated in the TNFR-KO mice, indicating that TNF serves a neuroprotective function. Their studies indicated that TNF protects neurons by stimulating antioxidative pathways. Injury-induced microglial activation was suppressed in TNFR-KO mice. They concluded that drugs which target TNF signaling pathways may prove beneficial in treating stroke or traumatic brain injury.

Marino et al. (1997) generated knockout mice deficient in TNF and characterized the response of these mice to a variety of inflammatory, infectious, and antigenic stimuli.

ALLELIC VARIANTS
(selected examples)

.0001 TNF RECEPTOR BINDING, ALTERED [TNF, LEU29SER]

Van Ostade et al. (1993) identified 2 cell lines with mutations in TNF that resulted in loss of almost all activity in the standard cytotoxic assay with the L929 murine fibrosarcoma cell line and were shown to have lost the binding affinity specifically for the TNF-R55 human receptor (191190). One of the mutants was found to carry a leu29-to-ser mutation and the other, an arg32-to-trp mutation (191160.0002). The remarkable ability of TNF, especially in combination with interferon, selectively to kill or inhibit malignant cell lines is unmatched by any other combination of cytokines. However, clinical trials have been disappointing, and it is estimated that a TNF dose would be effective only at 5 to 25 times the maximum tolerated dose. TNF binds to 2 types of receptors: the smaller, TNF-R55, is present on most cells and particularly on those susceptible to the cytotoxic action of TNF; the larger, TNF-R75 (191191), is also present on many cell types, especially those of myeloid origin, and is

strongly expressed on stimulated T and B lymphocytes. The selective binding of the mutant TNF to TNF-R55 might make it useful in cancer therapy.

.0002 TNF RECEPTOR BINDING, ALTERED [TNF, ARG32TRP]

See 191160.0001 and Van Ostade et al. (1993).

.0003 MALARIA, CEREBRAL, SUSCEPTIBILITY TO [TNF, -376G-A]

Knight et al. (1999) studied the significance of a single-nucleotide polymorphism (SNP) in the promoter region of TNF: a substitution of adenine for guanine at -376. Binding experiments showed that the transcription factor OCT1 (164175) can bind to site alpha of TNF, but that this binding is dependent on the presence of the TNF(-376A) allele. They showed, furthermore, that TNF(-376A) affects TNF expression in vitro. Since TNF has a pivotal role in human malaria, acting both to suppress parasitic growth and to cause clinical symptoms, Knight et al. (1999) investigated frequency of this allele in cases of cerebral malaria (see 248310) in the Gambia and in Kenya. They found an odds ratio (OR) of 4.3 for the -376A allele, compared with the control group. In both the Kenyan and the Gambian study populations, they found that the relatively rare -376A allele occurred only in individuals who also carried the more common -238A allele. The same had been reported in European populations. These results indicated that the -376 polymorphism occurred more recently in human evolution than the -238 polymorphism, and that it arose as a mutation of a haplotype bearing the -238A allele.

.0004 SEPTIC SHOCK, SUSCEPTIBILITY TO [TNF, -308G-A]

ASTHMA, SUSCEPTIBILITY TO, INCLUDED
HUMAN IMMUNODEFICIENCY VIRUS DEMENTIA, SUSCEPTIBILITY TO, INCLUDED

Mira et al. (1999) referred to the TNFA promoter polymorphisms at position -308 as TNF1 for guanine and TNF2 for adenine. In a multicenter study involving 7 institutions, they found a significant association between the TNF2 allele and susceptibility to septic shock and death from septic shock. The septic shock group was defined by the following 6 criteria within a 12-hour period: (1) clinical evidence of infection; (2) hyperthermia or hypothermia; (3) tachycardia; (4) tachypnea; (5) necessity for vasopressor to maintain systolic blood pressure; and (6) evidence of inadequate organ function or perfusion.

Moraes et al. (2001) found that the TNF2 polymorphism is significantly associated with a stronger response (Mitsuda reaction) to lepromin in borderline tuberculoid leprosy patients. Epigenetic factors such as a history of BCG vaccination or a reversal reaction, but not both, were also associated with boosted Mitsuda reactions. Moraes et al. (2001) concluded that augmented TNF production may be associated with the TNF2 allele and an increased granulomatous response.

Ma et al. (1998) found a higher frequency of the rare T2 TNFA polymorphism (-308G-A) in 43 Japanese Guillain-Barre syndrome (139393) patients who had had antecedent infection with C. jejuni than in 85 community controls.

Witte et al. (2002) evaluated the relation between the -308G-A promoter polymorphism and risk of asthma (600807) in 236 cases and 275 nonasthmatic controls. Logistic regression analyses indicated that having 1 or 2 copies of the -308A allele increased the risk of asthma (odds ratio = 1.58), the magnitude of which was increased when restricting the cases to those with acute asthma (odds ratio = 1.86, P =

0.04) or further restricting the subjects to those with a family history of asthma and those of European-American ancestry (odds ratio = 3.16, P = 0.04).

Quasney et al. (2001) stated that immunologic mechanisms resulting in macrophage infiltration and glial cell activation in the brain are thought to be involved in the pathophysiology of HIV dementia. Moreover, elevated levels of TNF-alpha have been found in the brains of patients with HIV dementia. In a study of 16 patients with HIV dementia, 45 HIV-infected patients without dementia, and 231 controls, they found an increased frequency of the -308A allele in patients with HIV dementia (0.28 vs 0.11 in controls and 0.07 in HIV patients without dementia). There were no individuals with the A/A genotype in either of the HIV-infected groups. Quasney et al. (2001) noted that the -308A allele is associated with higher TNF-alpha secretion in response to an inflammatory stimulus and that evidence has shown a role for TNF-alpha in neuronal damage, thus suggesting a genetic predisposition to the development of HIV dementia.

Cox et al. (1994) reported that the -308A allele has an increased frequency in type I diabetes mellitus (222100). Krikovszky et al. (2002) studied ambulatory blood pressure in 126 Hungarian adolescents with type I diabetes mellitus. They found that the prevalence of the -308A allele was higher in diabetic adolescents than in the Hungarian reference population. TNFA genotype was associated with both systolic and diastolic blood pressure values. The -308A allele carrier state appeared to be associated with lower systolic and diastolic blood pressure values.

.0005 VASCULAR DEMENTIA, SUSCEPTIBILITY TO [TNF, -850C-T]

McCusker et al. (2001) typed the -850C-T polymorphism in 242 patients with sporadic Alzheimer disease (104300), 81 patients with vascular dementia, 61 stroke patients without dementia, and 235 normal controls. The distribution of TNF-alpha genotypes in the vascular dementia group differed significantly from that in the stroke and normal control groups, giving an odds ratio of 2.51 (95% CI, 1.49-4.21) for the development of vascular dementia for individuals with a CT or TT genotype. Logistic regression analysis indicated that possession of the T allele significantly increased the risk of Alzheimer disease associated with the APOE4 (see 107741) allele (odds ratio of 2.73 (1.68-4.44) for those with APOE4 but no TNFA T vs 4.62 (2.38-8.96) for those with APOE4 and TNFA T).

SEE ALSO

Beutler et al. (1986); Broudy et al. (1986); Davis et al. (1987)

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